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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/670,096
Filing Date: September 26, 2000
Appellant(s): MANSFIELD ET AL.

Ian McLeod
For Appellant

EXAMINER'S ANSWER

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. However, the rejection under 35U.S.C. 112, first paragraph for lack of deposit information and the rejection under 35U.S.C. 112, second paragraph for lack of antecedent basis are withdrawn, in view of amendments and arguments of record. The only remaining issue is lack of enablement under 35U.S.C. 112, first paragraph.

(7) Grouping of Claims

Appellant's brief includes a statement that claim 1 stands or falls on its own, claim 21 and claim 2 each stands or falls on its own and provides reasons in support thereof. See 37 CFR 1.192(c)(7) and (c) (8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Liang et al. "Evidence that Surface Proteins Sn 14 and Sn16 of *Sarcocystis neurona* Merozoites Are Involved in Infection and Immunity." Infection and Immunity 1998; 66 (5) 1834-1838.

Hines et al "Immunization of Cattle with Recombinant *Babesia bovis* Merozoite Surface Antigen-1." Infection and Immunity 1995, 63(1) 349-352.

Cutler et al "Immunoconversion against *Sarcocystis neurona* in normal and dexamethasone treated horses challenged with *S.neurona* sporozoites." Veterinary Parasitology 2001, 95, 197-210.

Fenger et al "Epizootic Equine Protozoal Myeloencephalitis in a Farm" 1997, JAVMA 210(7), 923-927.

(10) Grounds of Rejection

The following ground(s) of rejection is applicable to the appealed claims:

Claims 1, 2 and 21 are rejected under 35 U.S.C. 112, first paragraph as containing subject mater which was not described in the specification in such a way so as to enable one skilled in

the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

Claim 1 is directed to a composition for treating an equid infected with *Sarcocystis neurona* comprising a mixture of isolated antibodies against a 16 + /-4 kD antigen of *Sarcocystis neurona* and isolated antibodies against a 30 +/- 4 kD antigen of *Sarcocystis neurona* wherein the antibodies are from serum of an animal immunized with the antigen and wherein the mixture pharmaceutically acceptable carrier.

Claims 21and 2 are directed to a method for treating an equid infected with *Sarcocystis neurona* comprising:
(a) providing a mixture of antibodies against a 16 +/- 4 kD antigen and a 30 +/-4 kD antigen both of which are specific to *Sarcocystis neurona,* wherein the antibodies are selected from the group consisting of serum from an animal immunized with the antigen and monoclonal antibodies from a hybridoma, and wherein the antibodies are in a pharmaceutically acceptable carrier; and (b) inoculating the equid with the antibodies to treat the equid, wherein the antibodies are monoclonal antibodies.

The instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention encompasses a composition and a method for treating an equid infected with *S.neurona* comprising polyclonal and monoclonal antibodies. The state of the prior art indicates that *S.neurona* sporozoites penetrate the horse's intestinal tract, enter vascular endothelial cells, and complete at least one merogonous (merozoite liberation) generation. After immune response is induced, merozoites may pass through the vascular endothelium of the blood-brain barrier into the immune privileged central nervous system, where they survive and horse develops clinical stage of Equine protozoal myeloencephalitis (EPM). The high rate of exposure to *S.neurona* and the relatively low incidence of clinical EPM indicate that most horses develop effective immunity (no clinical symptoms of disease) that may prevent merozoite entry into the central nervous system. The pathogenesis of Equine protozoal myeloencephalitis (EPM) caused by *S.neurona* is not fully known. The prevalence of *S.neurona* infection in horses was approximately 45% in surveys conducted in different parts of USA and clinical EPM occurs in only a small proportion of seropositive horses. Therefore, it is important and necessary to identify factors that govern progression from an apparent infection to clinically evident neurological disease, EPM (see page 198, first three paragraphs from Cutler et al 2001) in horses.

The specification asserts that the antibodies of the instant claims are intended for use as "pharmaceutical /therapeutics" useful for treating *S.neurona* infection in an equid. However, the specification does not teach any *in vivo* method using the claimed antibodies for treating EPM disease in horses. The treatment of *S.neurona* infection in an equid with antibodies is highly complex and unpredictable because relative to the infection, the development of clinical spreading of the disease i.e., merozoite entry into the central nervous system crossing blood brain barrier is not known as most of the horses develop immunity without EPM. Further, it is

not known in the art what causes the infection to spread into the central nervous system or the merozoite (asexual stage of parasite) entry into the central nervous system in spite of developing antibodies during infection. Further, the prior art does not teach administration of a mixture of isolated antibodies against a 16 kD antigen of *S. neurona* and isolated antibodies against a 30 kD antigen of *S. neurona* to an infected horse with EPM which would resolve the infection in CNS. This is very critical because horses do develop immunity during infection and all horses with infection do not show clinical signs of EPM. Thus there is a lack of understanding in the art with respect to the pathogenesis of *S.neurona* infection in horses that develop EPM.

As it appears that the knowledge of parasite invasion to CNS is very limited. Liang et al 1998 (Infection and Immunity; 66 (5) 1834-1838) teach that not all antibodies generated during infection will neutralize the merozoites *in vitro* and optimum inhibition required sensitization of merozoites in serum or CSF for at least 40 min, suggesting that maximum inhibition of parasite infection (infectivity as measured by neutralization assay) requires saturation with specific antibodies (see page 1837, left column, second paragraph). Further, Liang *et al* teach that '[A] although *S.neurona* was sensitive to specific antibodies, a 10-min exposure to antiserum was required to yield a significant reduction in parasite production (effect of trypsin digestion on parasite). This may partially explain why protective antibodies to some apicomplexan parasites are effective *in vitro* but not *in vivo*. Newly released parasites are exposed to serum for a shorter time *in vivo*, and the access of neutralization-sensitive epitopes to antibody may be limited' (page 1837, right column, 3rd paragraph in particular). Further, Liang *et al.* conclude while Sn 16 kD and Sn 14 kD antigens are expressed *in vivo,* further investigation of these candidate antigens is necessary for inclusion in a vaccine (page 1837, bridging paragraphs of first and second columns). The results of and conclusion by Liang *et al.* clearly indicate that *in vitro* data does not necessarily correlate to or is extendable *in vivo*. Since the claimed

invention clearly drawn to a composition or a method for treating an equid infected with *S. neurona,* whether the claimed composition prevents the spread of *S.neurona* infection to the nervous system so that horses do not develop EPM or inhibits the *S.neurona* infection in the CSF needs to be experimented.

The specification does not provide evidence that the claimed isolated antibodies (passive immunization with antibodies) prevent the spread of *S. neurona (merozoite)* to the nervous system. Furthermore, it is unclear whether such an immunotherapy can be used to treat all horses that are infected with *S.neurona* The specification does not have any evidentiary support to show which horses have been given this treatment or at what stage of the infection the horses have been treated with antibodies. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In light of the teachings of Liang et al that the ability of an antibody in neutralizing merozoites in *vitro* does not correlate to function *in vivo,* the instant specification has not given the necessary teaching to provide a link between the proposed antibody (uncharacterized) and treatment of the infection. In addition, the specific antibodies, which bind to 16kD and 30 kD antigens required to treat an equid infected with *S.neurona* are not characterized.

The high degree of unpredictability associated with the claimed composition or method underscores the need to provide teachings in the specification that would provide the artisan with specific treatment regimens that achieve a therapeutic benefit; however, the specification does not provide such guidance and fails to provide the necessary guidance. The specification only discloses that multiple isolates of merozoites have been obtained by culturing sporozoites from opossum (pages 37-44). However, the specification fails to show support for a composition for

treating an equid infected with *S.neurona* comprising a mixture of isolated antibodies against 16 kD and isolated antibodies against 30kD antigen and a method of treating an equid using these antibodies that would stop the infection (i.e., merozoite entry after crossing blood brain barrier) spreading to the brain. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for the claimed composition or a method that is required in this under developed art. The specification only teaches culturing sporocysts and merozoites. It is not clear whether or not all horses that are exposed to *S.neurona* infection are chosen to treat or those horses that show clinical signs of symptoms are treated since the naturally infected horses do develop antibodies to merozoites. Further, the specification fails to indicate that the claimed antibody is able to control the systemic infection from spreading to central nervous system after merozoites pass through the vascular endothelium of the blood-brain barrier that causes EPM.

In view of lack of support for passive immunization in the art and high degree of unpredictability that *in vitro* assays are associated/correlated with *invivo*, the amount of guidance provided by the specification (i.e., lack of working examples in the specification) and the nature of invention, the claimed composition to treat infection and a method of treating an equid with said composition are not sufficient for one skilled in the art to make use of the invention as claimed. Therefore a composition for treating infection and a method for treating an equid infected with *S.neurona* comprising a mixture of isolated antibodies against 16 kD and isolated antibodies against 30kD antigens must be considered highly unpredictable, requiring a specific demonstration of efficacy of the composition and a method using such composition in treating *S.neurona* infection.

While the immunological data of Liang et al strongly suggests that some cell surface antigens have no protective function, the immunizations of animals with uncharacterized mixture of (monoclonal) antibodies and expecting therapeutic effect needs to be experimented. Without necessary specific guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict the amount of composition for its intended use. Therefore, undue experimentation would be required to make and use the invention as broadly claimed.

(11) Response to Argument

Appellant's arguments filed in Appeals Brief December, 23, 2004 have been fully considered but they are not deemed to be persuasive.

Appellant states that the appellants believe that the specification provides enablement which is commensurate with the scope of claims 1, 2 and 21and when all of the evidence relating to the factors set forth in M.P.E.P. 2164.01(a) for determining whether disclosure satisfies the enablement requirement is considered, the evidence as whole shows that the scope of the claims are enabled. Appellant states that the specification (pages 13, 15 and 27, example 1) teaches that the 16kD and 30kD antigens are specific to *S.neurona* and are useful for producing vaccines. Vaccines can comprise antibodies that are polyclonal or monoclonal and the antibody vaccine can be used for therapeutic treatment of horses infected with *S.neurona*.

The examiner has reviewed the specification and found no support for the claimed invention. As a whole neither the specification nor the record indicates that the claims are enabled because while making antibodies are routine in the art but using them in a therapeutic treatment for horses infected with *S.neurona* would require undue experimentation as the claimed antibodies are not characterized including the binding characteristic to either 16kD or 30kD antigen.

Appellant agrees with the examiner that Liang et al teach that antisera from horses with EPM contain antibodies against immunodominant merozoite antigens 11, 14, 16 and 30kD from *S.neurona.* Liang et al indicate that for optimum inhibition the merozoites are required to be sensitized in serum or CSF for at least 40 minutes (see page 1837, 2nd paragraph, left column in particular). This may partially explain why protective antibodies to some apicomplexan parasites are effective *in vitro* but not *in vivo.* However, Appellant cites Hines et al (Infection. Immunity 1995, 63; 349-352) to support that a second antigen was required to be effective in protecting the immunized cattle against a challenge.

The examiner reviewed the article of Hines et al carefully and understands that the antibody mediated neutralization of merozoite infectivity in vitro, at least for merozoite surface antigen specific antibody (MSA-1) does not reflect in vivo protective immunity to babesiosis. Further, the art teaches the reason for failure of protection in vivo because (1) merozoites are exposed to serum for shorter periods of time in vivo and accessibility of neutralization sensitive epitopes to an antibody binding may be limited, (2) failure to induce sufficient antibody and (3) the relation of T helper subset in stimulating antibody response (see page 350, right column through page 351, left column in particular).

Thus the prior art teaches that there are many factors involved in vivo protection of babesiosis compared to in vitro conditions. The prior art suggests to include other parasite surface proteins such as MSA-2 in immunization protocol, which play critical role in host cell invasion. Appellant is comparing passive immunization (two antibodies given to an infected horse) with Hines active immunization (antigen is given directly) procedure that is not relevant to the claimed invention as these two methods of immunizations are practically different. Further, like Liang et al, Hines et al also supports the examiner's position that in vivo treatment does not correlate with the invitro assays and parasite host cell invasion is important in the treatment. The examiner is aware that multivalent vaccines provide better protection against parasitic diseases such as malaria. However, the present invention is related to passive immunization not an active immunization which requires more than one antigen.

Appellant agrees that most horses develop effective immunity that prevents merozoite entry into CNS and infected horses with EPM have antibodies against 11, 14, 16 and 30kD antigen. However, appellant states that antibodies to 30kD are not recognized as specific which suggests that 30kD antigen is common to all Sarcocystis spp and not unique to *S.neurona.* The appellants teach that horses make antibodies to 16 and 30kD antigens and such antibodies in CNS have neutralizing effect on merozoites (Table 1 in Appendix B - Declaration under 37 CFR 1.132). Therefore a person of ordinary skill in the art would more likely than not believe that a composition comprising the 16 and 30 KD antigens for treating horses infected with *Sarcocystis neurona* is effective for treating the EPM disease since the pathogenesis of the disease is not yet known in the art.

The examiner disagrees with the appellant because the Declaration does not provide any evidence that the claimed composition comprising said antibodies are useful for treating an equid infected with *S.neurona*. Further, the Declaration does not show that the antibodies would stop the spread of *S.neurona* infection to the nervous system (CNS) that causes EPM as appellant is claiming a method of treating an equid infected with *S.neurona*. Therefore, it is necessary to show the data in support of the treatment of horses with antibodies to 30kD and 16 kD. The Declaration provides evidence that CSF from infected horses contains antibodies to 16kD and 30kD and such antibodies neutralize the merozoites *in vitro* (neutralization assays) only.

The examiner disagrees with the Appellant on the issue that a composition comprising 16 kD and 30 kD antigens for treating horses infected with *Sarcocystis neurona* would be effective for treating the disease because Appellant's invention is not drawn to an active immunization with 16kD and 30kD antigens but rather drawn to passive immunization with a mixture of antibodies to treat the horses already infected with *S.neurona* infection. However, there is no support for passive transfer of antibodies in vivo. Further, the examiner has not rejected the claims solely based on *in vitro* neutralization assays as taught by Liang et al but raised the issue of unpredictability based on the lack of support in this undeveloped art as stated above and Appellant has not provided any evidence on the efficacy of these antibodies in treating infected horses as discussed above.

It is the position of the examiner that the art teaches that there is a high rate of exposure to *S.neurona* infection in horses and relatively low incidence of clinical EPM indicates that most horses develop an effective immunity that may prevent the entry of the merozoite

(asexual stage of parasite) into the central nervous system (see Liang et al 1998, page 1834, right column, first four lines in particular). It is known in the art that the parasite may express different surface antigens at different stages of *in vivo* (see Liang et al 1998, page 1837, last paragraph in particular) or *in vitro* development and some antigens expressed and function only in vitro. Such antigens are inappropriate for vaccine development. In addition, Fenger et al's teachings indicate that in case of EPM that the parasite continues to undergo merogony (see Fenger et al 1997, page 923, upper right column, first paragraph in particular) in CNS. Appellant's specification indicates (see example 3) that the merozoites used were obtained by growing excysted Opposum's (natural reservoir of *S.neurona*) sporocysts in equine dermal cells, which appears to be different from merozoites grown in CNS. Therefore the claimed antibodies to 16kD and 30kD antigens may not be able to pass the blood brain barrier and may not be able to eliminate merozoites in CNS, which is very important for the treatment. Thus, the antigens expressed in merozoites before EPM and after EPM are necessary and cannot be assessed with appellant's neutralization assay as indicated in the Declaration. The state of the art suggests that treatment with drugs like pyrimethamine –sulfonamide in combination with a competent immune response eventually eliminates merozoites (see Fenger et al 1997, page 926, right column, fourth paragraph in particular). Therefore, it is important to provide evidence that the treatment with the claimed antibodies is sufficient to prevent entry of the parasite into CNS or elimination of merozoites already present in CNS.

Appellant on page 15 and 16 of the Brief states that Liang et al does not demonstrate that the horses with clinical signs resembling EPM were actually infected with *Sarcocystis neurona* and it is not known whether any of the Liang samples reported contain only antibodies against 30 kD antigen (Figure 2 in Liang 1998 article). The horses might have been infected

with another Sarcocystis species, which induces an antibody that reacts non-specifically with the 30 kD antigen from *Sarcocystis neurona*. For example, the appellants show Patent No. 6,153,394 to Mansfield reference which indicate that the serum from horses known not to be infected with *Sarcocystis neurona* contain antibodies to 30kD antigen.

The examiner would like to bring appellant's attention to page 10 of the brief where appellant states that Liang et al teach that antisera from horses with EPM contain antibodies against immunodominant merozoite antigens 11, 14, 16 and 30kD from *S.neurona* and on the other hand Appellant does not believe that the horses with clinical signs resembling EPM were actually infected with *S. neurona*. The examiner understands that there are some cross reactive antibodies to 30kD antigen, however Liang et al do not depend solely on 30kD antigen but clearly teaches merozoite 11 kD, 14 kD and16 kD antigens are specific for *S.neurona* and pointed for the first time that 30kD antigen from *S.neurona* may be cross reactive with other Sarcocystis spp in diagnosing 30 kD antigen as specific. Based on Liang"s teaching the appellants show in Patent No. 6,153,394 to Mansfield that the serum from horses known not to be infected with *S. neurona* contain antibodies to 30kD antigen and developed a diagnostic assay by absorbing the *S.neurona* antigen with non labeled antibodies to proteins from Sarcocystis spp other than *S.neurona* from a species of mammal other thanequine prior to reaction with the equine antibodies so that nonspecific binding of equine antibodies is inhibited to thereby detect the *S.neurona*.

Appellant is misinterpreting Liang et al's teaching that antibodies to 30kD are not neutralizing. Liang et al clearly recognizes the problem for lack of neutralization with antibodies to 30kD and explains that the serum or CSF contains antibodies to 30kD antigens from other *Sarcocystis* species (see page1837, left column, and first paragraph). Therefore, Liang et al do

not teach that antibodies to 30kD antigen of *S.neurona* are not neutralizing *in vivo* rather teaches the presence of cross reacting antibodies and such antibodies could not neutralize the merozoite in an *in vitro* assay.

The examiner has not rejected the claims solely based on *in vitro* neutralization assays as taught by Liang et al but raised the issue of unpredictability based on the lack of support in this undeveloped art as stated above and Appellant has not provided any evidence on the efficacy of these antibodies in treating infected horses.

Appellant on page 17 states that passive immunization with antibodies can be used for treating an equid in the early stages of infection and thus can improve horses resistance to *S.neurona* at a critical early stage when the presence of *S.neurona first* suspected and points to the Table 1 on page 5 of the Declaration that the addition of CSF containing antibodies against 16kD and 30kD antigens have neutralizing effect. Further, Appellant states that the data provided would lead a person of ordinary skill in the art to conclude that the claimed composition and method likely to be beneficial to an equid infected with *S.neurona.* Appellant also provided Appendix D unpublished manuscript as supporting evidence.

The examiner understands that the addition of CSF containing antibodies against 16kD and 30kD antigens have neutralizing effect on dermal cells in an *in vitro* assay. However, the examiner does not understand what Appellant meant by "improve resistance" when animal is already infected with *S.neurona.* The Declaration does not indicate horses treated with mixture antibodies do not develop EPM or eliminate the merozoites in CNS. The examiner carefully reviewed the unpublished manuscript Appendix D (no page numbers) and noted that the source and nature of the monoclonal antibodies are not yet (see under monoclonal antibodies, page 4 as per examiner's counting) known and therefore, one skilled in the art would not be able to use

the composition and method as claimed. Further, the article is yet to be completed and published.

Review of the present specification, the art of record, and a search of the art on passive immunotherapy indicate that the composition and method have not been identified nor described. The treatment of *S.neurona* infection in an equid is highly complex and unpredictable because the specification does not provide an enabling disclosure for treating equid with *S.neurona* following administration of any and all monoclonal antibodies in the instant invention. The specification does not provide evidence that the claimed antibodies either treat the infection in central nervous system or prevent the spread of *S. neurona* to the nervous system (EPM disease), which support such an assertion. The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific regimens that achieve a benefit; however, the specification does not provide such guidance and fails to provide the necessary guidance.

Further, as taught by Liang et al 1998 (Infection and Immunity; 66 (5) 1834-1838) it is apparent that all antibodies generated during an infection to various antigens will not neutralize all antigens. The results of and conclusion by Liang et al clearly indicates that in vitro data does not necessarily correlate to or is extendable in vivo. While the immunological data of Liang et al strongly suggests that all surface antigens have no protective function and therefore, the antibodies, which bind to such surface antigens, would not be expected to have any therapeutic effect. Thus, there is no nexus between the treatment of infected horses with claimed antibodies and an expected therapeutic effect.

Without necessary specific guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition/method for its intended use. Therefore, undue experimentation would be required to make and use the invention as broadly claimed. Appellant has no evidence such a composition is prepared and horses have been treated *S.neurona* infection. Appellant is claiming a therapeutic composition and a method of treatment *S.neurona* infection based on theoretical /hypothetical knowledge of making therapeutic antibodies. In view of the lack of guidance, working examples (see page 19, second paragraph, first two lines), breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to practice the full scope of the invention as broadly claimed.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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